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Pharmacokinetics, *in-vitro* activity, therapeutic efficacy and clinical safety of aztreonam vs. cefotaxime in the treatment of complicated urinary tract infections

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The minimal inhibitory concentrations (MICs) of aztreonam and cefotaxime were determined against 400 isolates from urological in-patients with complicated and/or hospital acquired urinary tract infections (UTI). Against the Gram-negative rods the activities of both antibiotics were comparable except for higher activity of aztreonam against *Pseudomonas aeruginosa*. The pharmacokinetic study in nine elderly patients showed a prolonged plasma half life of aztreonam (2·7 h) as compared to younger volunteers (1·6–1·9 h).

In a prospective randomized study 39 urological patients with complicated and/or hospital acquired UTI were treated with 1 g aztreonam or cefotaxime iv twice daily for 4 to 15 days. Cure was obtained in 5 out of 18 patients in the aztreonam and 7 out of 20 patients in the cefotaxime group. There were 3 superinfections, 7 relapses and 3 reinfections in the aztreonam group and 1 failure, 1 superinfection, 6 relapses and 5 reinfections in the cefotaxime group. There was no significant difference in therapeutic efficacy between the two antibiotics. Both antibiotics were tolerated well and seem to be equally effective in the treatment of complicated UTI caused by sensitive organisms.

Introduction

Aztreonam is a new monocyclic β-lactam antibiotic (Sykes *et al.*, 1981) with high activity against aerobic Gram-negative bacteria. Previous studies have shown that aztreonam is eliminated predominantly through the kidneys and that its serum half-life is about 1·6–1·9 h (Swabb *et al.*, 1982, 1983 *a, b, c,* Wise *et al.*, 1982). The present paper describes the *in-vitro* activity of aztreonam compared with that of cefotaxime against bacterial isolates from urological patients with complicated and/or hospital acquired urinary tract infections (UTI), the pharmacokinetics of aztreonam and the therapeutic efficacy of aztreonam compared with that of cefotaxime in the treatment of complicated and/or hospital acquired UTI.

Materials and methods

Antibiotics and chemicals

The antibiotics were supplied as follows: aztreonam by Squibb-Heyden, Munich, Germany, and cefotaxime by Hoechst AG, Frankfurt, Germany. Antibiotic medium 1

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and Mueller-Hinton broth were obtained from Difco Laboratories, Detroit, Michigan, USA and Merck, Darmstadt, Germany. Nutrient broth and blood agar base no. 2 were from Oxoid Deutschland GmbH, Wesel, Germany.

Inulin was obtained from Laevosan, Linz, Austria; Conray 70^{R} (a mixture of iothalamic acid, sodium salt and megluminate) and pure iothalamic acid were from Byk-Gulden, Konstanz, Germany.

In-vitro *study: clinical isolates*

In-vitro minimal inhibitory concentrations (MICs) of aztreonam and cefotaxime were determined against 400 strains isolated from the urine of urological in-patients with complicated and/or hospital acquired UTI (bacterial counts $\geq 10^5$ cfu/ml). Only patients with monoinfections were included in the study.

Subjects

Group I. Nine elderly patients (8 male, 1 female) with a mean age of 72·6 years (range 64–82 years), a mean body weight of 65·3 kg (range 53·1–79·8 kg) and a mean height of 1·63 m (range 1·54–1·69 m) were recruited for the pharmacokinetic study. The subjects had serum creatinine levels < 15 g/l. Written informed consent was obtained.

Group II. The subjects of the clinical study were 39 urological patients (27 male, 12 female) between the ages of 18 and 83 years. They had complicated and or/hospital acquired UTI and significant bacteriuria with urinary counts of $\geq 10^5$ cfu/ml. All patients gave informed written consent.

Pharmacokinetic study

Aztreonam, 1 g, was administered intravenously over 3 min in 100 ml of sterile physiological saline containing 5·0 g inulin and 20 ml Conray 70^{R}, corresponding to 13·2 g iothalamic acid. Blood samples were taken immediately before and 5, 10, 20, 30, 45, 60, 90 min and 2, 4, 6 and 8 h after the dose. Urine samples were collected before and at the following intervals: 0 to 2; 2 to 4; 4 to 6; 6 to 8 and 8 to 12 h after the administration of aztreonam. The urine volumes were measured and aliquots were taken for assay.

Clinical study

The subjects of the clinical study group were randomized and treated intravenously either with aztreonam (AZ) or with cefotaxime (CTX), 1 g bd, over 4–15 days. The patients had not received antimicrobial therapy within 4 weeks before the study. Bacterial urine cultures were performed prior to the therapy, during therapy, one or two days after treatment (post-treatment), and one to four weeks (one patient six weeks) later (follow-up). In addition urinalysis, haematology (erythrocyte, leucocyte and platelet counts) and chemistry profiles (creatinine, BUN, total bilirubin, alkaline phosphatase, SGOT, SGPT) were followed in each patient pre- and post-treatment. The patients were closely watched for local and systemic adverse reactions to the antibiotics. Bacteriological cure implied eradication of the primary offending organism and the absence of superinfection or reinfections with different species during the following therapy. The pathogens, isolated by standard microbiological techniques, were checked for purity on blood agar plates and their identities were confirmed by Gram's stain, colonial morphology and by use of the API-20 systems (API bioMerieux GmbH, Nürtingen, Germany).

Determination of the minimal inhibitory concentration (MIC)

For the *in-vitro* study the activities of aztreonam and cefotaxime were determined by the agar dilution technique using doubling dilutions of the antibiotics from 128 to 0·015 mg/l in Mueller-Hinton agar (Merck) as the test medium. Inoculum size was 10^4 cfu using a multipoint inoculator (Dynatech). For the clinical study the activities of aztreonam and cefotaxime were assayed by the broth dilution method in Mueller-Hinton broth (Difco) as the test medium. The isolated clinical strains were grown overnight in nutrient broth (Oxoid) to give a viable count of about 10^9 cfu/ml. The final inoculum size was 5×10^5 cfu/ml. After 18 h of incubation at 37°C the minimal inhibitory concentrations (MICs) were read by eye. The MIC was defined as the lowest concentration of the antibiotic that prevented visible growth of the micro-organism.

Assay of aztreonam

Aztreonam concentrations in serum and urine samples were determined microbiologically by the agar plate diffusion technique. The agar medium was antibiotic medium 1 and the test organism was *Escherichia coli* 6311/65 (Hoescht AG). Serum urine standards ranging from 0·5 to 10·0 mg/l were prepared in human serum and in phosphate buffered saline, respectively. Samples and standards were assayed in triplicate. After incubation overnight at 37°C the inhibition zones were measured with an accuracy of 0·1 mm.

Assay of inulin

Inulin in serum and urine was estimated chemically according to Heyrovsky's method (Heyrovsky, 1956). The chemical estimation of inulin is based on the hydrolysis of inulin to fructose, which is determined photometrically by the colour formed upon reaction with indole-3-acetic acid in hydrochloric acid. The interference by glucose was found to be negligible.

Assay of iothalamic acid

Iothalamic acid was determined by HPLC according to a published procedure (Kees, Grobecker & Naber, 1984) with minor modifications. In brief, serum (400 µl) was deproteinized with acetonitrile (400 µl). The latter was removed by extraction into dichloro-methane (2 ml) and an aliquot of the aqueous phase containing the iothalamic acid was injected into the chromatographic system. Urine was centrifuged and injected directly after dilution (1:20) with water. The liquid chromatograph consisted of a pump M 6000 A, an autoinjector WISP 710 B, a fixed wavelength detector M 440, operating at 254 nm, a data module M 730 and a system controller M 720, all from Waters, Ass., D-6236 Eschborn, Germany. For separation a HIBAR^R column (ID 125 × 4 mm) was used prefilled with LiChrosorb^R RP 18 silica (particle size 5 µm) from Merck, D-6200 Darmstadt, Germany. The mobile phase was a mixture of 880 ml water, 120 ml acetonitrile, 1·40 g sodium acetate trihydrate, and 450 mg tetrabutylammonium hydrogensulphate. The pH was adjusted to 4·8 with acetic acid. The flow rate was maintained at 1·0 ml/min resulting in a back pressure of 110 bar and a retention time of 4·0 min for iothalamic acid.

Pharmacokinetic analysis

The pharmacokinetic parameters were obtained from serum concentrations by use of an open two compartment model and the following equation for fitting the experimental data: concentration $= A.e^{-\alpha t} + B.e^{-\beta t}$.

Table I. Minimal inhibitory concentrations (MICs) of aztreonam (AZ) and cefotaxime (CTX) against 400 bacterial isolates from the urine of patients with urinary tract infections

Species		Minimal inhibitory concentration (mg/l)													
		≤0·016	0·03	0·06	0·125	0·25	0·5	1	2	4	8	16	32	64	≥128
E. coli (137)*	AZ	9	49	56	12	4	1		3	2		1			
	CTX	8	60	49	13		3	2	2						
Pr. mirabilis (53)	AZ	53													
	CTX	21	28	3	1										
Klebsiella spp. (28)	AZ	3	11	4	2	3	2	1			1			1	
	CTX	1	15	6	2	2		1		1					
Pseudomonas spp. (20)	AZ								2	10	6	1	1		
	CTX									1	1	1	13	3	1
Enterobacter spp. (10)	AZ	2	2	2		1			1	2					
	CTX	2		1	2	1	1				1	1	1		
Ser. marcescens (5)	AZ			1	1				1	2					
	CTX					1		1				1	2		
Acinetobacter spp. (6)	AZ								1			4	1		
	CTX	1								2		2	1		
Citrobacter spp. (4)	AZ		2	2											
	CTX		1	2	1										
Prov. stuartii (1)	AZ	1													
	CTX	1													
M. morganii (1)	AZ	1													
	CTX			1											
Enterococci (63)	AZ														63
	CTX														63
Staph. epidermidis (49)	AZ														49
	CTX					2	13	7	8	2	9	4			4
Staph. aureus (16)	AZ														16
	CTX						2	3	6	3	2				
Streptococci (6)	AZ												1	1	4
	CTX	2	1	1		1	1								
Total (400)	AZ	69	64	65	15	8	3	1	8	16	7	6	3	2	133
	CTX	36	105	63	19	7	20	14	16	9	13	9	17	3	69

*Number of isolates.

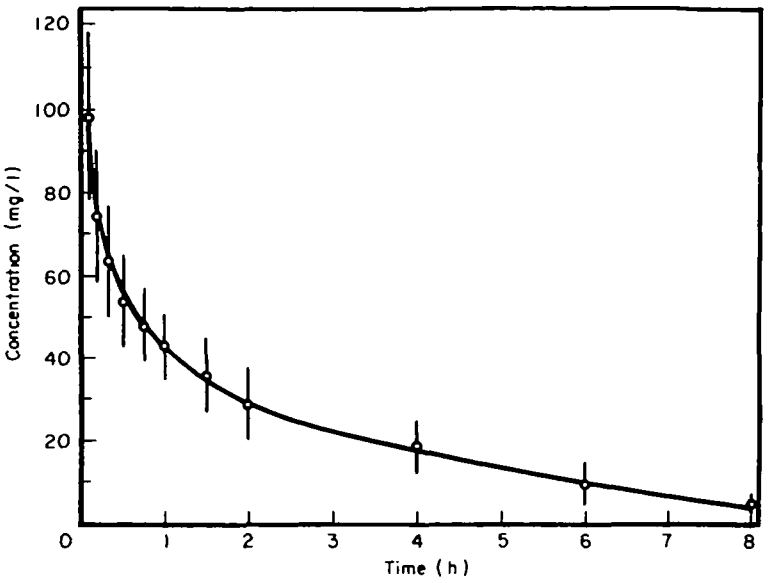

Figure 1. Serum concentrations of aztreonam in nine elderly patients after intravenous administration of 1 g aztreonam (mean ± S.D.).

Results

In-vitro study

The MIC values of aztreonam and cefotaxime for the 400 isolates cultured from the urine are shown in Table I. The MICs of aztreonam against all but nine of the 265 Gram-negative isolates were 8 mg/l or lower. The MICs against all but two of the 134 Gram-positive isolates were 128 mg/l or higher. Cefotaxime inhibited 90·2% of the Gram-negative and 47·0% of the Gram-positive isolates at 8 mg/l or lower.

Pharmacokinetic study

The serum concentrations after injection of 1 g of aztreonam are shown in Figure 1. The mean ± S.D. (range) serum half-life amounted to 2·7 ± 0·8 h (1·8–4·3 h). The mean ± S.D. (range) urinary concentrations of aztreonam were: 0–2 h 1598 ± 554 mg/l (906–2716 mg/l), 2–4 h 1195 ± 598 (647 ± 2293), 4–6 h 964 ± 564 (272–1799), 6–8 h 443 ± 198 (109)–795), and 8–12 h 244 ± 140 mg/l (7·9–449 mg/l).

In Table II the calculated pharmacokinetic parameters of aztreonam, inulin and iothalamic acid are listed. The mean serum half-life of aztreonam (2·7 h) and iothalamic acid (2·7 h), as well as the volume of distribution (each 27·5% of body weight) were slightly higher than the corresponding parameters of inulin which is a marker for the extracellular space. On the other hand, total clearances were of the same order (around 90 ml/min). The mean urinary recovery (Figure 2) within 12 h was 70% for aztreonam and nearly 90% for the other two compounds. The high standard deviation of the urinary recovery of aztreonam is striking.

The mean ± S.D. (range) urinary recovery of aztreonam with respect to inulin was 82 ± 36% (33–143%) whereas that of iothalamic acid was 103 ± 5% (96–111%).

There was no statistically significant linear correlation between the serum clearances of aztreonam and inulin, but there was between iothalamic acid and those of inulin ($r = 0{\cdot}91$; $P < 0{\cdot}05$).

Table II. Pharmacokinetic parameters (mean ± S.D.) of aztreonam, inulin and iothalamic acid in nine elderly patients after simultaneous intravenous injection of 1 g aztreonam, 5 g inulin, and 13·2 g iothalamic acid

		Aztreonam ($n=9$)	Inulin ($n=9$)	Inulin ($n=7$)	Iothalamic acid ($n=7$)
Plasma half-life:	$T^{\beta}_{1/2}$(h)	2·67 ± 0·79	2·18 ± 0·36	2·18 ± 0·39	2·68 ± 0·63
Volume of distribution	$V_{d,ss}$(l)	17·5 ± 4·6	13·8 ± 2·1	14·4 ± 1·4	18·4 ± 2·16
	$V_{d,ss}$(%kg)	27·5 ± 8·9	21·3 ± 3·8	21·6 ± 3·8	27·5 ± 4·08
Area under the curve	$AUC_{0\to\infty}$(mg·h/l)	208 ± 67	967 ± 273	904 ± 273	2464 ± 571
Plasma clearance	Cl_{tot}(ml/min)	86·9 ± 24·0	91·5 ± 22·7	95·4 ± 20·1	93·6 ± 22·4
	Cl_{tot}(ml/min/70 kg)	95·2 ± 28·4	98·6 ± 22·8	98·8 ± 14·6	96·5 ± 14·6
Renal excretion	$U_{0\to12\,h}$(% of dose)	72·0 ± 45·4	84·5 ± 17·5	86·4 ± 19·3	89·0 ± 19·5

*One patient did not receive iothalamic acid; another patient was injected with a substance which interfered with the assay of iothalamic acid.

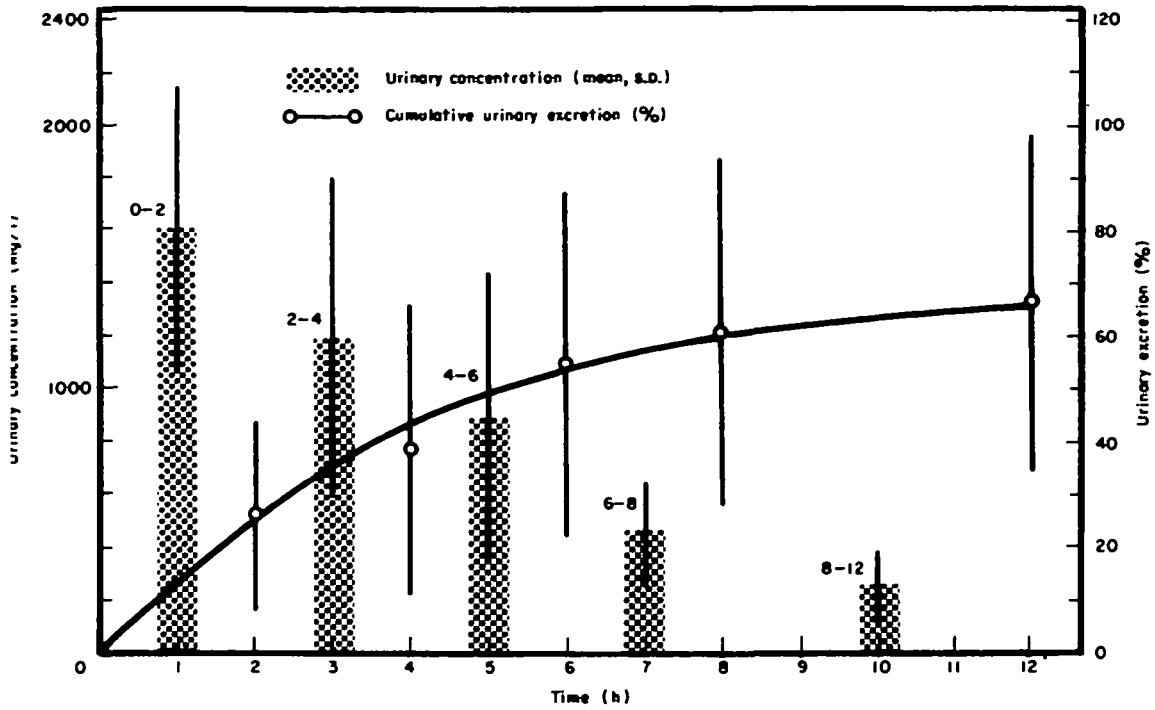

Figure 2. Urinary concentrations (mean ± S.D.) and cumulative urinary excretion (% of dose injected) in nine elderly patients after intravenous administration of 1 g aztreonam.

Clinical study

In the patients with UTIs the following causative organisms (AZ/CTX) were found: *E. coli* (8/9), *Proteus mirabilis* (3/5), *Pseudomonas aeruginosa* (1/3), *Klebsiella pneumoniae* (5/0), *Pr. vulgaris* (1/1), *Providencia stuartii* (0/1), *Enterobacter* sp. (1/1), *Citrobacter freundii* (0/2). There were three mixed infections (1/2) with *E. coli* and enterococci or two different *Proteus* spp. respectively.

The causative organisms were eradicated in all patients in the aztreonam group and in 19 of 20 patients in the cefotaxime group (Table III).

One to two days after treatment significant bacteriuria was still found in three out of 19 patients in the aztreonam and in two out of 20 in the cefotaxime group. Definite cure (no significant bacteriuria in post treatment or follow up among specimens) was obtained in five out of 18 patients in the aztreonam and in seven out of 20 patients in the cefotaxime group. There were three superinfections (different species present one to two days after therapy), seven relapses (same species present again at follow up), three reinfections (different species found at follow up) in the aztreonam group (one patient was not assessable); and one failure (same species one to two days after therapy), one superinfection, six relapses and five reinfections in the cefotaxime group. There was no significant difference in therapeutic efficacy between the two antibiotics.

In a total of nine patients (aztreonam 5, cefotaxime 4) all with pyuria, enterococci were cultured from the urine on at least two occasions after the antibacterial treatment. Seven of these patients were treated because of urinary tract infections which occurred postoperatively. One patient had stones in the bladder and one patient a renal tumour.

Table III(a). Bacteriological findings in the urine of 19 patients pre- and post-treatment with aztreonam

No.	Sex M/F	Age (Yrs)	Pre-treatment			Post-treatment			Follow up			Result
			Days of Rx	Pathogen	MIC (mg/l)	Day after Rx	Pathogen	MIC (mg/l)	Day after Rx	Pathogen	MIC (mg/l)	
01	M	79	7	*E. coli*	0·06	1	—	—	8	Enterococci	>128	Reinfection
07	F	56	5	*E. coli*	0·015	1	—	—	10	*E. coli*	0·06	Relapse
12	M	73	6	*E. coli*	0·25	1	—	—	5	*E. coli*	<0·015	Relapse
19	F	64	4	*E. coli*	0·125	1	*Enterococci*	>128	Inapplicable			Superinfection
22	M	74	5	*E. coli*	n.d.	1	—	—	7	—	—	Cure
				Enterococci	>128							
29	M	70	6	*E. coli*	0·06	2	—	—	n.d.			Not evaluable
34	M	74	7	*E. coli*	0·125	1	—	—	9	*E. coli*	0·125	Relapse
37	F	77	7	*E. coli*			—	—	7	—	—	Cure
14	M	85	5	*K. pneumoniae*	n.d.	1	—	—	17	*K. pneumoniae*	0·125	Relapse
18	M	81	5	*K. pneumoniae*	0·06	1	—	—	8	*K. pneumoniae*	0·125	Relapse
23	M	66	5	*K. pneumoniae*	0·125	1	*Enterococci*	>128	Inapplicable		n.d.	Superinfection
41	M	81	7	*K. pneumoniae*	n.d.	1	—	—	12	—	—	Cure
43	M	81	7	*K. pneumoniae*	0·06	1	—	—	9	10^6 not identif.		Reinfection
27	M	81	7	*Pr. mirabilis*	n.d.	1	—	—	8	Enterococci	>128	Reinfection
35	F	50	7	*Pr. mirabilis*	0·06	1	—	—	9	*Pr. mirabilis*	⩽0·015	Relapse
39	M	69	15	*Pr. mirabilis*	<0·015	2	—	—	10	—	—	Cure
04	M	71	8	*Pr. vulgaris*	<0·015	1	Enterococci	n.d.	Inapplicable			Superinfection
15	M	78	5	*Ps. aeruginosa*	4	1	—	—	8	*Ps. aeruginosa*	8	Relapse
10	M	76	5	*Ent. cloacae*	n.d.	1	Candida	—	7	—	—	Cure

Table III(b). Bacteriological findings in the urine of 20 patients pre- and post-treatment with cefotaxime

No.	Sex M/F	Age (Yrs)	Days of Rx	Pre-treatment		Post-treatment			Follow up		
				Pathogen	MIC (mg/l)	Day after Rx	Pathogen	MIC (mg/l)	Day after Rx	Pathogen	MIC (mg/l)	Result
03	F	48	5	*E. coli*	0·06	1	—	—	41	—	—	Cure
11	M	60	5	*E. coli*	0·06	2	—	—	28	*E. coli*	n.d.	Relapse
13	F	73	5	*E. coli*	n.d.	2	—	—	6	—	—	Cure
17	M	78	5	*E. coli*	0·125	n.d.			9	*K. pneumoniae*	0·06	Reinfection
21	M	80	7	*E. coli*	0·06	2	*Enterococci*	>128	Inapplicable			Superinfection
32	F	63	7	*E. coli*	0·06	1	—	—	7	—	—	Cure
				Pr. mirabilis	<0·015							
33	F	30	14	*E. coli*	0·06	1	—	—	10	—	—	Cure
40	M	74	7	*E. coli*	0·06	1	—	—	14	*E. coli*	0·125	Relapse
44	F	18	7	*E. coli*	0·06	1	—	—	8	—	—	Cure
08	F	72	5	*Pr. mirabilis*	0·015	1	—	—	7	Enterococci	>128	Reinfection
				Pr. vulgaris	n.d.							
				E. coli	0·06							
16	M	71	5	*Pr. mirabilis*	<0·015	1	—	—	7	—	—	Cure
26	M	83	7	*Pr. mirabilis*	0·015	1	—	—	7	*Staph. epidermidis*	1	Reinfection
28	F	69	7	*Pr. mirabilis*	<0·015	1	—	—	8	*Enterococci*	n.d.	Reinfection
05	M	72	10	*Ps. aeruginosa*	n.d.	1	*Ps. aeruginosa*	32	Inapplicable			Failure
24	M	78	5	*Ps. aeruginosa*	32	1	—	—	8	*Ps. aeruginosa*		Relapse
38	M	71	7	*Ps. aeruginosa*	>128	1	—	—	6	—	—	Cure
20	M	77	5	*Ent. aerogenes*	0·125	n.d.			4	*Ent. aerogenes*	0·125	Relapse
02	F	60	11	*Citro. freundii*	1	1	—	—	9	Enterococci	>128	Reinfection
30	M	78	7	*Citro. freundii*	0·25	1	—	—	7	*Citro. freundii*	0·125	Relapse
09	M	69	7	*Prov. stuartii*	n.d.	2	—	—	21	*Prov. stuartii*	0·25	Relapse

This last patient was treated with aztreonam for four days because of an *E. coli* infection. Since the patient remained febrile and superinfection with enterococci occurred, treatment was successfully changed to bacampicillin.

Both antibiotics were well tolerated so that it was not necessary to stop therapy because of adverse reactions. There were no biochemical signs or symptoms of renal, hepatic or haematological toxicity.

Discussion

The therapeutic spectrum of cefotaxime includes the majority of staphylococci but not enterococci. All Gram-positive strains are resistant to aztreonam. The Gram-negative strains cultured from the urine of 400 urological in-patients were comparably sensitive to aztreonam and cefotaxime. Aztreonam, however, showed a greater activity against *Pseudomonas* species.

The pharmacokinetics of aztreonam exhibited a prolonged plasma half life (2·7 h) in elderly patients as compared to healthy volunteers (1·6–1·9 h). In an earlier study of cefotaxime pharmacokinetics in geriatric patients (Naber & Adam, 1980), a prolonged half life of about two hours was also found. In both the studies plasma concentrations showed a fairly wide range. In elderly patients with prolonged half lives of aztreonam and cefoxatime, doses given twice daily should be sufficient for the treatment of UTI. The total plasma clearances of aztreonam, inulin and iothalamic acid are very comparable, indicating that the major route by far for the renal excretion of aztreonam is via glomerular filtration. Since at low concentrations the chemical analysis of inulin is difficult, plasma concentrations could only be measured up to 4–6 h after iv administration of 5 g. Therefore in the study iothalamic acid was also administered. This compound, clinically used as contrast medium for urography, is as suited as inulin for the determination of glomerular filtration rate (Sigman, Elwood & Knox, 1965). After injection of 20 ml Conray 70^{R}, corresponding to 13·2 g iothalamic acid, plasma concentrations can easily be measured by HPLC up to 24 h after injection. During and immediately after therapy high success rates were achieved with both the antibiotics. However, definite cure (no bacteriuria found within follow up period), could only be observed in about one-third of the patients regardless of the antibiotic used. Comparable results were obtained in two other studies of urological patients treated with different antimicrobial compounds (Naber & Bauernfeind, 1982; Naber & Wittenberger, 1985). Relapses and reinfections are common phenomena following the treatment of complicated UTI. In these cases underlying anatomical or functional abnormalities may serve as a nidus of infection and prevent complete eradication of bacteria.

The high rate of reinfections with enterococi (nine cases) occurred predominantly in postoperative patients. This may have been due to the epithelial lesions present within the urinary tract and the resistance of this species against both of these antibiotics.

Aztreonam and cefotaxime were tolerated well without any side effects. Both the antibiotics seem to be equally suited for the treatment of complicated UTIs caused by sensitive organisms. However, one should be aware of possible reinfections with enterococci.

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